REMARKS

1. Amendments to the Claims

Claims 1, 2, 5, 19-22, 24, 25, and 27 are rejected. Claims 7-18 are withdrawn. Claims 3 and 4 have been cancelled. New claims 29 and 30 are herein added.

Claims 1 and 19 have been amended. Claim 20 has been incorporated into claims 1 and 19. Accordingly, claim 20 has been cancelled. Claims 1 and 19 have also been amended to add antecedent basis for various terms.

Claim 2 has been amended to provide antecedent basis.

Claims 22-28 have been amended in view of the cancellation of claim 20 to change their dependency.

New claims 29 and 30 have been added. Support for claim 29 is found in the Specification at page 32 lines 18-21. Support for claim 30 is found in the Specification at Examples b-4 and B-5.

Accordingly, no new matter has been added.

2. Written Description

The Examiner rejects claims 21-22, 24-25, and 27 under 35 U.S.C. § 112 as lacking sufficient written description. The Examiner indicates that because the Specification does not disclose the relationship between the structure and function of the cell cycle protein, one of skill would not have found that Applicants had possession of the entire genus at the time of filing. Applicants respectfully disagree and submit that the Specification amply supports variants of the claimed sequences.

"[T]he determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science and technology, the predictability of the aspect at issue, and other considerations appropriate to subject matter. *See, e.g., In re Wallach,*

378 F.3d 1330, 1333-34 (Fed. Cir. 2004) (an amino acid sequence supports "the entire genus of DNA sequences" that can encode the amino acid sequence because "the state of the art has developed" such that it is a routine matter to convert one to the other)." *Capon v. Eschar,* 418 F.3d at 1357 (Fed. Cir. 2005). The Examiner is further cautioned that there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure. *Falkner v. Inglis,* 79 USPQ2d 1001, 1008 (Fed. Cir. 2006). "The forced recitation of known sequences in the patent disclosures would only add unnecessary bulk to the specification." *Id.* at 1008.

In the present situation, Applicants submit that the claims directed to 90% or at least 95% sequence identity to SEQ ID NOs: 1 or 2 are amply supported by adequate written description because he Specification teaches both the structure and the related function of the genus of the claimed Tob family proteins and Caf family proteins. The Specification teaches that both Tob family proteins and Caf family proteins halt the cell cycle at G0/G1 or G2/M transitions. (Specification, page 1, lines 21-23; page 2, lines 15-18). The Specification teaches that the Tob family of proteins "usually comprises a homologous region consisting of about 110 amino acid residues having homology with the amino acid sequence shown in SEQ ID NO: 1 in an N-terminal region of the amino acid sequence thereof." (Specification, page 14, lines 16-20). Two "highly homologous regions" are disclosed, Box A (or GR Box) (SEQ ID NO: 2) and Box B (SEQ ID NO: 3). (Specification, page 15, lines 7-15). Applicants provide multiple specific examples of the location of Boxes A and B in various Tob proteins. For instance the Specification discusses the exact position of Boxes A and B in multiple Tob proteins:

hTob is disclosed at page15, lines 19-20

hTob2 is disclosed at page 15, lines 20-21

Pc3 is disclosed at page 15, line 21-22

hAna is disclosed at page 14, lines 23-25

mBtg3 is disclosed at page 14 line 25 to page 15, line 1, and

hPc3b is disclosed on page 15, lines 1-3.

The Specification also discusses additional Tob family proteins B9.10, Pc3K, and B9.15. (Specification, page 17, lines 16-17). Sequences for these Tob family proteins can be found in the Specification at page 22, lines 7-19, frequently for both human and mouse. Thus, the Specification explicitly discloses the highly homologous regions and the sequences of *at least* nine Tob family proteins. Moreover, the Specification indicates that these structural features are common to Tob family proteins. (Specification, page 15, lines 11-12).

With regard to the Caf family proteins, the Specification discloses Caf1, Caf2, and POP2. (Specification, page 17, lines 17-18).

The Specification also has working examples using hTob, hCaf1, both together, and two tyrosine kinases: Lck and LckYF. (Specification, Examples A1-3, A 4, B4, and B-5).

Furthermore, as demonstrated by the disclosures in the Specification, the existing knowledge in the particular field, and the maturity of the science and technology is such that one of skill would have recognized that Applicants had possession of a genus of sequences having 90% or at least 95% sequence identity to SEQ ID NOs: 1 or 2 and that they could be transformed into yeast and used in a method for the screening of screening for a physiologically active substance.

Thus, Applicants submit that there is more than adequate written description for the Tob family and the Caf family (Claim 20). Applicants respectfully request that the rejection be withdrawn.

3. Enablement

The Examiner rejects claims 21-22, 24-25, and 27 under 35 U.S.C. § 112 as not enabled. The Examiner has not rejected claim 20 for enablement.

Enablement requires that one of skill be able to make and use the invention without undue experimentation. Enablement is a factual inquiry, where the Examiner weighs factors such as:

(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands,* 8 USPQ 1400, 1404 (Fed. Cir. 1988).

Experimentation is not undue if it is routine in the art. Even if a skilled artisan would have to conduct experiments and go through "trial and error" to reproduce the invention, that fact does not invalidate the patent under section 112. "A patent is invalid only when those skilled in the art are required to engage in undue experimentation to practice the invention." *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1557, 220 USPQ 303, 316, (Fed.Cir. 1983).

a. The Breadth of the Claims

Applicants submit that the claims are not unduly broad. The claims are directed to a method of screening for a physiologically active substance where a protein having at least 90% or 90% sequence identity to amino acid sequences SEQ ID NOs: 1, 2, or 4 is transformed into yeast. The degree of variation is at maximum 10 percent. Thus, Applicants submit that the claims are not unduly broad.

b. The Predictability in the Art

Applicants submit that the art of transformation in yeast is predictable, as is evidenced by the disclosures in the Specification and the knowledge in the art, discussed below.

c. The Relative Skill in the Art

Applicants submit that the relative skill in the art is high.

d. The Amount of Guidance and Working Examples

Applicants submit that the Specification provides more than ample guidance to one of skill in the art to enable them to make sequences having at least 90% or 95% sequence identity to SEQ ID NOs: 1, 2, or 4 and to use these sequences in a method of a method of screening for a physiologically active substance. As discussed above, the Specification teaches multiple examples of specifically identified regions in the Tob family proteins which need to be conserved (that is SEQ ID NOs: 1 and 2 are these highly conserved regions), and provides multiple examples of the families of proteins. The Specification also indicates how much variation is permitted. The Specification also gives the sequence for a Caf family protein. (SEQ ID NO: 4). Further, the Specification discloses at least three working examples falling within the scope of the Claims. (Specification, Examples A1-3, A 4, B4, and B-5, disclosing the working examples of hTob, hCaf1 and both together).

Applicants also provide culture conditions and methods for determining the growing state of the yeast. (See, e.g., Specification, page 30, beginning at line 7, see also Examples). Furthermore, Applicants provide multiple parameters to measure the growing state of the yeast, such as monitoring a change in turbidity of a yeast culture medium, a morphological change, a change in wet-weight of the yeast, a change in the endogenous enzyme activity of the yeast, or a change in the amount of endogenous protein of the yeast. (Specification, page 31, lines 17-22).

e. <u>The Amount of Experimentation Needed</u>

Applicants submit that the amount of experimentation needed to use the claimed method would not be undue. Specifically, it is routine to transform yeast, and screen to determine if they grow. In view of the known sequences, the limited variability of those sequences, the known structure of the proteins, and the routine screening required to transform the yeast and determine whether they grow. Applicants submit that the amount of experimentation would not be undue.

Applicants submit that the breadth of the claims, the predictability and relative skill in the art, the guidance and working examples in the Specification, and the amount of experimentation needed all weigh in favor of a conclusion that the claims are enabled. Accordingly, Applicants submit that one of skill would understand how to make and use the claimed invention. Applicants request that the rejection be withdrawn.

4. Indefiniteness

The Examiner rejects claims 1 and 19 and dependent claims 2-5 and 20-28 as indefinite. The Examiner rejects claims 1 and dependent claims 2-5 for the recitation of "cultured." Similarly, the Examiner rejects claims 19 and dependent claims 20-28 for the recitation of the terms "protein" and "vector." The Examiner indicates that there is insufficient antecedent basis for these limitations.

Applicants have amended claims 1 and 19 to account for the terms "cultured" and "protein," thereby obviating the rejection. Applicants request that the rejection be withdrawn.

5. Anticipation

The Examiner rejects claims 1-3 and 5 under 35 U.S.C. § 102(b) as anticipated by Meier (U.S. Application Number 2005/0118576). Applicants note that Meier is not prior art under § 102(b) as the Meier reference had not been published for over at year at the time of filing of the parent PCT application.

Applicants have amended claim 1 to incorporate non-rejected claim 20. Accordingly, Applicants submit that claim 1 is not anticipated by Meier. Applicants request that the rejection be withdrawn.

6. Obviousness

The Examiner rejects claims 1-5 and 19-20 under 35 U.S.C. § 103(a) as unpatentable over Meier in view of Bounaga (WO 01/20020) and Naiehe (WO 02/68687) as evidenced by Nakahama (U.S. Patent 5,182,195).

Applicants respectfully submit that the Examiner has merely provided a conclusory statement that one of skill in the art would substitute the lack of oxidative respiration for the intracellular G0/G1 cell cycle checkpoint blocker of Bounaga. However, rejections on

obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *KSR Int'l Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007). The Examiner has failed to provide a reason why one of skill in the art would want to have lowered cell growth rate. Thus, the Examiner's rejection fails at the outset.

Also, one of skill in the art would not combine Bounaga with Meier to obtain the method wherein the protein is involved intracellular signaling of G0/G1 phase of mammal cell growth. Specifically, the method of Meier is intended to "determine chemical compounds to be tested with pharmacological utilities at the basis of anti-oxidative or metal chelating properties," or with "diseases caused by the pathological accumulation of iron or copper in certain tissues of the body." (Meier, page 2, right column, paragraphs [0017] and [0018]). Meier does not attempt to determine a G0/G1 cell cycle checkpoint. Naiehe does not remedy this deficiency as it merely discloses that Tob family proteins have an action on cell growth. Neither Naiehe, nor Nagahara indicate that one of skill in the art would substitute the anti-oxidative or metal chelating properties of Meier with growth arrest proteins of Bounaga. Thus, the Examiner has failed to establish that one of skill in the art would substitute a Tob family or Caf family protein out of an infinite number of possible growth affecting proteins in the method of Meier to obtain the claimed method.

Accordingly, Applicants request that the rejection be withdrawn.

Applicant believes the pending application is in condition for allowance and requests entry of the above amendments and allowance of the claims.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mary M.H. Eliason Reg. No. 58,303 at the telephone number (858) 792-4982, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____

Gerald M. Murphy, Jr.
Registration No.: 28,977
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road
Suite 100 East
P.O. Box 747
Falls Church, Virginia 22040-0747
(858) 792-8855
Attorney for Applicant